

REMARKS

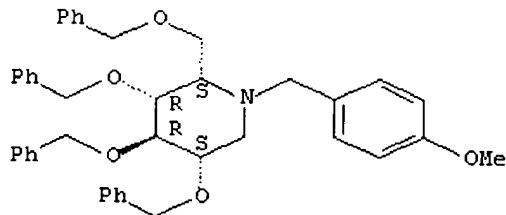
Claims 1-4, 6, 7 and 23-38 are pending in the current application. Claims 5, 8-22 were previously cancelled. Claims 7 and 24-38 are withdrawn. Claims 1-4, 6 and 23 have been rejected. For editorial purposes, claims 1, 3 and 4 have been amended to read “in free or pharmaceutically acceptable salt form”. Claims 1, 3 and 4 have also been amended to delete the term “prodrug”. It is believed no new matter has been added.

Claim Rejections under 35 U.S.C. § 112

Claims 1-4 and 6 have been rejected under §112, first paragraph for purportedly failure to enable the prodrugs of the invention. Without agreeing as to the accuracy of the Examiner’s statements or arguments, Applicants have amended claims 1, 3 and 4 to remove the offending language and to expedite allowance of the claims. Withdrawal of the rejections under 35 U.S.C. § 112, first paragraph is respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-4, 6 and 23 under 35 U.S.C. § 103(a) as being allegedly obvious in view of WO 02/055498 (hereinafter “WO ‘498”). In particular, the Examiner identified the compound of Example 15 on page 26 of WO ‘498:



as the closest compound. The Examiner argued that the only differences between the claimed compounds and that in WO ‘498 are that the benzyl group on the N1-position of the piperidine ring of the claimed compound is substituted with a C₄₋₅-alkoxy group while the benzyl group of the compound of WO ‘498 is substituted with a C₁-alkyl (e.g., methyl) group. In addition, the Examiner argued that the WO ‘498 reference teaches that the compound, when absent the protecting group, is the free hydroxy. As such, the Examiner concluded that the claims are obvious.

Applicants respectfully disagree. It is well established that a disclosure of a generic formula does not by itself render obvious a species of that genus. *See In re Baird*, 16 F.3d 380, 382 (Fed. Cir. Jan. 19, 1994) ('The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.') (citing *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992); *See also* MPEP 2144.08. In addition, “[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.”). *In re Baird*, 16 F.3d at 383. To begin a proper obviousness analysis of structurally similar chemical compounds, the Examiner must first identify the lead compound in the prior art. *See Eisai Co. LTD v. Dr. Reddy's Laboratories, LTD.*, 533 F.3d 1353, 1359 (Fed. Cir. July 21, 2008) (“a prima facie case of obviousness for a chemical compound [] begins with the reasoned identification of a lead compound.”). Once identified, the Examiner must also provide adequate support in the art for the change of the lead compound to the claimed invention. *See Takeda Chemical Industries, LTD v. Alpharm PTY., LTD*, 492 F.3d 1350, 1356 (Fed. Cir. June 28, 2007) (“[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of ‘adequate support in the prior art’ for the change in structure.”).

Here, WO ‘498 generically discloses 2-hydroxymethyl-3,4,5-trihydroxypiperidine compounds having a (2S,4R,5S) configuration useful as GCS inhibitors, wherein the configuration at the 3-position may be (S) or (R). Applicants admit that the claimed compounds of Formula I fall within the generic disclosure of WO ‘498. However, nothing in WO ‘498 suggests that, of all the possible substituents, that the C₄-alkoxy substituent on the N1-benzyl is preferred, rendering the selection of the claimed compound of Formula I or Formula III obvious. The Applicants strongly disagree with the fact that the deprotected compound of example 15 is the structurally closest compound as the Examiner claimed. This disagreement is based on the following grounds:

- Firstly, this view can be considered as hindsight since the compound of example 15 of WO ‘498 is presented as a “protected intermediate”. A protected intermediate, if deprotected, gives an intermediate, which should, by definition, not be considered by one skilled in the art as a biologically active compound. Besides, it would not have been clear for one skilled in the art which compound the deprotected intermediate would be: is it the compound of

example 15 from which the benzyl groups have been removed, or the same compound from which the 4-methoxy-benzyl group has been removed, or the same compound from which the benzyl groups and the 4-methoxy-benzyl group have been removed? Again, only hindsight can help one skilled in the art to arrive at a compound close to the compounds of claim 1 of the instant patent application. As a result, for one skilled in the art, the intermediate corresponding to the compound of example 15 of WO ‘498 cannot be the closest prior art compound.

- The compound sharing most structural features with the compounds of claim 1 of the instant patent application would therefore rather be the compound of example 9 of WO ‘498, which is not a protected intermediate unlike the compound of example 15 of WO ‘498. The compound of example 9 differs from the compounds of claim 1 of the instant patent application in that:
 - it has a phenethyl-derived side chain instead of a benzyl-derived side chain on the nitrogen atom of the iminosugar core; and
 - the phenyl ring of the iminosugar side chain is unsubstituted, whereas it bears a C₄₋₅ alkoxy side chain in 4 position in the compounds of claim 1 of the instant patent application.

In other words, the compounds of claim 1 of the instant patent application actually differ from the compound of example 9 of WO ‘498 by several structural features (i.e. benzyl instead of phenethyl attached to the nitrogen of the iminosugar core, substituted phenyl ring instead of unsubstituted phenyl ring in the side chain attached to the nitrogen of the iminosugar core, substitution by a C₄₋₅ alkoxy group on the phenyl ring of said side chain, substitution in 4 position of the phenyl ring of said side chain) and not only a single structural feature. Even so, identification of the compound of example 9 as the lead compound, however, is only possible with the hindsight knowledge of the current claimed invention.

- Alternatively, the one skilled in the art, in looking at WO ‘498, particularly Table 2 on page 27, may also be inclined to think that compounds of Examples 2 and 3 of WO ‘498 as the lead compounds since those two compounds have good IC₅₀ and selectivities against human GCS. These compounds, however, do not contain the benzyl substituent on the piperidine

ring at all. Therefore, one skilled in the art who knew of WO '498 and sought new GCS inhibitors, would not make further derivatives of the benzyl-substituted piperidine compounds as he would not expect those compounds to be more interesting than those of Examples 2 and 3 of WO '498. As one can see on Table 2 of WO '498, the compounds of Examples 2 and 3 have an IC₅₀ of 10.6μM and 4.0μM respectively against human GCS. The compounds of Examples 1 and 2 of the current invention, on the other hand, have an IC₅₀ of 0.15μM and 0.42μM respectively against GCS. Nothing in WO '498 suggests that substituting the piperidine ring with a 4-(C₄₋₅salkoxy)-benzyl would give a 10-70 fold increase in GCS activities. It is therefore respectfully submitted that the compounds of the currently claimed invention have unexpected results and finding that these had interesting GCS inhibition properties was certainly novel and unobvious at the filing date of the instant patent application. In view of the arguments, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

Claim Rejections for Double Patenting

The Examiner provisionally rejected claims 1-4, 6 and 23 as being unpatentable over claims 1-10 and 13 of copending application number 10/522,208 (the '208 application) on the ground of nonstatutory obviousness type double patenting for the compounds of the two cases are allegedly not patentably distinct.

Applicants respectfully disagree. The '208 application, although claims (2S,3S,4R,5S) 2-hydroxymethyl-3,4,5-trihydroxypiperidine compounds having a substituted benzyl substituent at the 1-position of the piperidine ring, the benzyl substituent is allowed to be substituted with very many different substituents, but a C₄₋₅salkoxy group. As discussed above, "a prima facie case of obviousness for a chemical compound [] begins with the reasoned identification of a lead compound." *Eisai*, 533 F.3d at 1359. In addition to the lead compound, the art must provide some kind of suggestion for the change in the structure to arrive at the claimed invention. Here, nothing in the '208 application suggests that C₄₋₅salkoxy is desirable. It is respectfully submitted that the Examiner has not met her burden of showing prima facie obviousness to support the nonstatutory obviousness type double patenting rejection. Reconsideration and withdrawal of this rejection is earnestly and respectfully requested.

This response is filed within three months from the date of the mailing of the non-final office action dated April 9, 2010, which response is due July 9, 2010, it is believed this response is timely and no fees are required. If this is not correct, however, please charge any additional fees, or credit any overpayment, to Deposit Account No. 50-4255.

Respectfully submitted,

Dated: July 9, 2010

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